UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/626,879	07/25/2003	Jang Han	072121-0189-Reg	1049

27476 7590 05/23/2006

Chiron Corporation
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097

EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 05/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/626,879	HAN ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/04,11/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 7-25-03.

Claims 1-66 are pending in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 3, 24-27, 30, 31, 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 is not further limiting from claim 2. ?). Appropriate clarification is required.

Claim 31 is not further limiting than claim 30. ?). Appropriate clarification is required.

The metes and bounds of claim 45 cannot be determined because the term "corresponds to" (line 4) is vague and unclear. ?). Appropriate clarification is required.

In claim 24, it is unclear what is meant by a double stranded RNA fragment containing at least one strand that spans the genome of a target agent (*e.g.*, Do both strands span the genome, but only one is modified? Or does one strand span the genome, and the other merely compliment a part of that strand?). Appropriate clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-66 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to compositions and methods of inactivating a virus in a patient comprising administration of a double stranded RNA or siRNA molecule that targets the genome of and inactivates a target virus, which siRNA molecules are optionally modified, and which optionally are at least 80% identical to siRNA5, siRNAC1, C2, BB1, 5B2 or 5B4 or target a conserved nucleotide sequence necessary for viral (e.g. HCF) replication, or which comprises siRNA generated from a larger RNA construct with at least one strand that spans the genome of a target agent of a virus. The specification and claims do not adequately describe the distinguishing features or attributes concisely shared by the members of the claimed genera, which are broadly drawn to any siRNA sharing at least 80% identity to viral target genes and that provide for the function claimed, of inactivating any virus in a patient, and which optionally target any conserved nucleotide sequence necessary for viral replication or which are generated from a larger construct that comprises at least one strand that spans the genome of any target agent of any virus. The genera claimed embrace a multitude of

sequences, and the disclosure fails to provide a representative number of species for the genus that provides for the function claimed, *i.e.* that any virus in a patient. The specification teaches particular siRNA constructs that target specified regions of HCV or luciferase in vitro. These teachings, however, are not representative of the broad genera drawn to siRNA molecules that target the genome of and inactivate any target virus, which siRNA molecules are optionally modified, and which optionally are at least 80% identical to siRNA5, siRNAC1, C2, BB1, 5B2 or 5B4, or target a conserved nucleotide sequence necessary for viral (e.g. HCF) replication, or which comprise at least one strand that spans the genome of a target agent of a virus.

The disclosure does not clarify the common attributes or provide a representative number of species for adequate description of the encompassed genera of sequences that provide for the function claimed, of inactivating a virus in an organism. Concise structural features that would distinguish structures within the claimed genera of molecules from those outside of the genera are missing from the disclosure. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genera claimed. Thus, Applicant was not in possession of the broadly claimed genera.

Claims 1-23, 28-42, 45, 46, 54-56, 64-66 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the in vitro targeting and inhibition of expression of HCV or luciferase using particularly described siRNA molecules, does not reasonably provide enablement compositions and methods for

inactivating any virus in an organism comprising the administration of the broad genera of compounds claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with this claim.

The claims are drawn to compositions and methods of inactivating a virus in a patient, or treating a patient, comprising administration of a double stranded RNA or siRNA molecule that targets the genome of and inactivates a target virus, which siRNA molecules are optionally modified, and which optionally are at least 80% identical to siRNA5, siRNAC1, C2, BB1, 5B2 or 5B4 or target a conserved nucleotide sequence necessary for viral (e.g. HCF) replication.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of treatment in organisms that involves the delivery of nucleic acid molecules to appropriate cells or tissues in an organism. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of in vivo efficacy. (A. Branch, Trends in Biochem. Sci. 23: 45-50, *see* entire text for Branch; S. Crooke, Antisense Research & Application, Chapter 1, pp. 1-50, especially at 34-36).

Likewise, Peracchi cautions investigators in the field of gene therapy about the problems of achieving in vivo efficacy using nucleic acid based approaches. Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy: "A crucial limit of ribozymes in particular, and of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross biological membranes, and therefore to enter the cells where they are supposed to operate...cellular uptake following systemic administration appears to require more sophisticated formulations... the establishment of delivery systems that mediate efficient cellular uptake and sustained release of the ribozyme remains one of the major hurdles in the field." (A. Peracchi et al, Rev. Med. Virol. 14: 47-64, especially at 51).

Agrawal et al also speak to the unpredictable nature of the nucleic acid based therapy field thus: "It is therefore appropriate to study each ... oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide (S. Agrawal et al., Molecular Med. Today, 6: 72-81 at 80). Cellular uptake of oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense." Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of ... oligonucleotides in vitro and in vivo (see Agrawal et al especially at pages 79-80; *see* Chirila et al., Biomaterials, 23: 321-342 in its entirety, especially at 326-327 for a general review of the important and inordinately difficult challenges of the delivery of therapeutic oligonucleotides to target cells).

See Opalinska (Nature Reviews, Vol. 1, pages 503-514, 2002) for a review of the unpredictabilities associated with the in vivo efficacy of double stranded oligonucleotides for target gene inhibition: "Although conceptually elegant, the prospect of using nucleic acid molecules for treating human malignancies and other diseases remain tantalizing, but uncertain." (3rd full paragraph on p. 503). "...it is widely appreciated that the ability of nucleic acid molecules to modify gene expression in vivo is quite variable, ant therefore wanting in terms of reliability." (1st full paragraph on p. 511).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of inactivating any virus in vivo comprising the administration of modified siRNA. The specification teaches the targeting and inhibition of HCV or luciferase in vitro comprising the administration of particularly described siRNA. The specification fails to teach the in vivo delivery and inactivation of any virus using the broad genera of compounds claimed.

One skilled in the art would not accept on its face the examples given in the specification of the in vitro inhibition of HCV or luciferase expression as being correlative or representative of the successful inactivation of any virus in an organism comprising the administration of any double stranded RNA or siRNA molecule that targets the genome of and inactivates any target virus, which siRNA molecules are optionally modified, and which optionally are at least 80% identical to siRNA5, siRNAC1, C2, BB1, 5B2 or 5B4 or target a conserved nucleotide sequence necessary

for viral (e.g. HCF) replication, or which comprises at least one strand that spans the genome of a target agent of a virus. This is in view of the lack of guidance in the specification and known unpredictability associated with predetermining the efficacy of nucleic acid delivery and appropriate expression whereby virus inactivation for any virus is provided in an organism. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with in vivo delivery and subsequent inhibition of any virus in an organism upon administration of siRNA, and specifically regarding the instant genera of siRNA broadly claimed.

The breadth of the claims and the quantity of experimentation required. The claims are broadly drawn to compositions and methods of inactivating a virus in a patient comprising administration of any double stranded RNA or siRNA molecule that targets the genome of and inactivates any target virus, which siRNA molecules are optionally modified, and which optionally are at least 80% identical to siRNA5, siRNAC1, C2, BB1, 5B2 or 5B4 or target a conserved nucleotide sequence necessary for viral (e.g. HCF) replication, or which comprise at least one strand that spans the genome of a target agent of any virus. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells or tissues harboring the target virus in an organism whereby any virus is inactivated. Since the specification fails to provide any particular guidance for the in vivo delivery and inactivation of any virus in an organism, and since determination of the factors required

for in vivo success are highly unpredictable, it would require undue experimentation to practice the invention over the broad scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4, 7-11, 14-17, 20-23, 28-32, 35-40, 43, 45-47, 51, 53-57, 62 and 64 are rejected under 35 U.S.C. 102(e) as being anticipated by Kay et al.

Kay et al (US 2003/0153519) teach the inactivation of HCV in an organism comprising the administration of siRNA (or an expression vector encoding the siRNA) to an organism or to a host cell, which siRNA specifically targets HCV, and which siRNA is optionally modified at the 2' position with a methyl or methoxyethyl group (see the abstract; figures 1-5; pages 11-17, claims 1-37).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-11, 14-40, 43, 45-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kay et al as applied to claims 1-4, 7-11, 14-17, 20-23, 28-32, 35-40, 43, 45-47, 51, 53-57, 62 and 64 above, in view of the combined teachings of Elbashir et al, Fosnaugh et al, Morrisey et al and Tuschl et al, and further in view of Noonberg et al and Baracchini et al insofar as the claims are drawn to methods of generating siRNA between 21-23 nucleotides in length from longer RNA constructs in the presence of dicer (as part of the RISC complex), as well as being drawn to compositions and methods for inactivating a virus in a patient or in vitro comprising administration of a double stranded RNA or siRNA molecule that targets the genome of and inactivates a target virus, which siRNA molecules are optionally modified at the 2' position with a methoxy or fluoro group, and further comprise a cholesterol moiety, or which siRNA are optionally in expression vectors comprising a H1 or U6 promoter, expressed as a single,

self complementary molecule, or which sense and antisense strands are expressed from separate promoters.

Kay et al are relied upon as set forth in the 102 rejection above.

Kay does not teach methods of generating 21-23 nucleotide length siRNA molecules in the presence of dicer, now does Kay teach the incorporation of 2'-fluoro modified groups into the siRNA molecules, or siRNA further comprising cholesterol groups, nor the expression of siRNA from expression vectors comprising U6 or H1 promoters, expressed either as separate self complementary strands or as one, self complementary strand.

Elbashir et al (EMBO J., vol. 20, No. 23, pages 6877-6888, 2001) teach methods of target gene inhibition in embryo lysates comprising siRNA molecules comprising 2'-deoxy and 2'-O-methyl substitutions. Elbashir et al teach a correlation between the placement of 2'-substitutions on the oligonucleotides and retaining siRNA activity (see esp. the abstract on p. 6877, fig. 8 and text on p. 6885).

Fosnaugh et al (US 2003/0143732) teach various motifs and configurations of 2'-modifications, including fluoro or methoxyalkyl groups of various alkyl chain lengths, and which oligonucleotides optionally further comprise, in addition to different motifs of differing 2'-substituent containing motifs, internucleotide linkage modifications comprising phosphorothioate internucleotide linkages, and which oligonucleotides optionally further comprise 3'-and/or 5'-terminal caps and optionally including inverted deoxy abasic moieties on the termini, and the effect of arrangements of these different modifications on siRNA ability to bind to and inhibit target gene expression in the

presence of RISC. Fosnaugh et al also teach compositions comprising modified and unmodified siRNAs and RISC for target gene inhibition see p. 1, 3-4, 6-9, p. 16 and figures 4 and 5, claim 30).

Morrissey et al (US 2003/0206887) teach various ways of designing and optimizing 2'-O-modifications on siRNA, including fluoro or methoxyalkyl groups of various alkyl chain lengths, and abasic, inverted abasic termini and 5' and 3' capped termini, and the effect of various motifs or arrangements of these 2'substitutuents and modified phosphorothioate internucleotide linkages on target gene inhibition by siRNA in compositions further comprising RISC (see fig. 4 and 5, page 1, right col., p. 6, right col., p. 9, p. 20-21, claims 20-25).

Tuschl et al teach the generation of siRNA molecules from longer dsRNA in the presence of dicer, and the use of 21-23 nucleotide siRNA's to target and inhibit the expression of a target gene in vitro (see the abstract, figures 6, 7, 10-12, pages 1-3, 5, 6 (example 1), pages 10-14 (examples 2-4).

Noonberg (USPN 5,624,803) teach the expression of small inhibitory RNA molecules in mammalian target cells using expression vectors comprising H1 or U6 promoters (see the abstract and figures 11-27, see also col. 13, 15-16, col. 24-25, col. 27, col. 29, claims 2, 3, 7, 14-16).

Baracchini et al teach the expression antisense oligonucleotides comprising cholesterol moieties for facilitating target cell entry and which oligonucleotides optionally comprise various modifications, including 2'-fluoro modified groups (see esp. col. 6 and 7).

It would have been obvious to one of ordinary skill in the art to generate small double stranded siRNA molecules to target genomic sequences of HCV because Kay et al teach the polynucleotide sequence of the target HCV genome as well as the design and use of various siRNA molecules that target and inhibit HCV in vitro and in vivo. It would have been obvious to generate smaller siRNA fragments from larger RNA molecules because Tuschl et al, Elbashir et al and Fosnaugh et al teach the generation of these smaller double stranded siRNA molecules upon incubation of larger RNA molecules in the presence of ATP and dicer (as part of the RISC complex). One would have been motivated to generate siRNA fragments between 21-23 nucleotides in length because it was well known in the art that siRNA of this size range successfully inhibit the expression of a target gene of known sequence, including various regions of the HCV genome, as taught previously by Kay et al, Tuschl et al and Elbashir et al. One of ordinary skill in the art would have been motivated to target and inhibit the expression of HCV because this virus is known to infect humans and siRNA is well known in the art as a potential therapeutic agent for virus inactivation. It would have been obvious to incorporate various motifs and configurations of 2'-modifications, including fluoro or methoxyalkyl groups of various alkyl chain lengths, and which oligonucleotides optionally further comprise, in addition to different motifs of differing 2'-substituent containing motifs, internucleotide linkage modifications comprising phosphorothioate internucleotide linkages, and which oligonucleotides optionally further comprise 3'- and/or 5'-terminal caps and optionally including inverted deoxy abasic moieties on the termini into siRNA molecules for enhancing their target binding and stability, yet

minimizing inactivation of the siRNA ability to inhibit target gene expression because Elbashir et al, Fosnaugh et al and Morrissey et al all teach the designing and testing of various arrangements of modified siRNA for their ability to inhibit target gene expression, and Baracchini et al teach the incorporation of various modifications, including 2'-alky, methoxy or fluoro groups for enhancing oligonucleotide stability. It would have been obvious to incorporate cholesterol moieties onto the oligonucletoides because this has been taught previously by Baracchini for enhancing target cell uptake. One of ordinary skill in the art would have expected that the siRNA modified at appropriate configurations would provide target gene cleavage in the presence of an appropriate target gene sequence and in the presence of appropriately modified siRNA and RISC. One of ordinary skill in the art would have produced various motifs as a matter of design choice and optimizing 2'-O modified motifs within the SiRNA while maintaining its SiRNA activity would have been a matter of design choice. One of ordinary skill in the art would have designed and tested such modification motifs because it was well known in the art at the time of the instant invention that incorporation of 2'-O-methoxy alky or 2'-deoxy, or 2'-fluoro modifications at appropriate positions within the siRNA allows for enhanced oligonucleotide stability, target binding and the trigger of target gene degradation by RISC. One of ordinary skill in the art would also have been motivated to incorporated 5', and/or 3' caps, including abasic and inverted abasic nucleotide or other terminal well known caps because these modifications were well known in the art to protect oligonucleotides from degradation, as taught previously by Morrissey. It would have been obvious to one of ordinary skill in

the art to express siRNA from expression vectors comprising U6 or H1 promoters because these promoters were well known in the art, as taught by Noonberg et al, for the use in expression vectors for use in mammalian cells. One of ordinary skill in the art would have been motivated to express these siRNA molecules as separate, self complementary molecules or as a single, self complementary molecule because it was well known in the art that siRNA will self anneal upon appropriate expression in a target cell either as separate strands or as a single strand, and preference would have been a design choice used routinely in the art. One would have expected that these expressed strands would form self complementary double strands in a host or in vitro. Therefore the instant invention as a whole would have been prima facie obvious to one of ordinary skill at the time it was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. 1.6(d)). The official fax telephone number for the Group is **571-273-8300**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
5-17-06